is achieved by proper selection of the vinyl acetate (VA) content of the copolymer in addition to selection of the proper annealing conditions. In general, the membrane permeability decreases as the VA content of an EVA membrane decreases. Preferred annealing conditions according to this embodiment comprise an annealing temperature of about 45 - 75° C, most preferably about 52° C - 72° C, for a period of about 1 hour - 72 hours, most preferably 2-36 hours, and a VA content of 4 - 18%, most preferably 5 - 12%.

[00049] Differential scanning calorimetry (DSC) analysis may be used to determine the extent of membrane annealing and may be performed by procedures well known in the art. According to the preferred embodiments comprising an EVA copolymer rate controlling membrane, significant changes in the DSC profile are noted at annealing temperatures greater than about 60° C. At these temperatures, as seen in Figs. 5 and 6, the primary peak (T_m) is observed at about 98° C and remains substantially consistent at various annealing temperatures. However, the secondary peak, observed to appear at about 51° C for a non-annealed EVA membranes (9% vinyl acetate) (FIG. 5), appears at a higher temperature upon annealing at temperatures of about 40° C and greater (second peak at 71° C for an EVA (9% vinyl acetate) membrane annealed at 60° C for 2 hours as seen in Fig. 6). Preferred embodiments for EVA copolymer rate controlling membranes are directed to rate controlling membranes exhibiting DSC profiles having the secondary peak at a temperature within the range of about 51 - 80° C, most preferably 56 - 75° C. Additionally, a third, less significant peak is observed for annealed EVA , preferably within the range of about 32 - 40° C.

[00050] According to the preferred embodiments comprising polyurethane membranes, DSC analysis showed that an increase in annealing temperature caused a slight increase in the melting temperature. Similarly, a slight increase in moisture content from 0 to 1% caused a slight increase in melting temperature. It is preferred according to this embodiment to anneal at dry conditions.

[00051] Rate controlling membranes subjected to the annealing process of this invention overcome the disadvantages of those of the prior art. According to one embodiment, membrane annealing according to this invention surprisingly results in rate controlling membranes having enhanced permeabilities to drugs compared to membranes not treated in accordance with this invention. This is contrary to expectations of lower drug permeabilities due to the higher density of the annealed rate controlling membrane. For example, the density and crystallinity of a polymer are among the factors influencing the polymer's permeability coefficient. In general, the higher the density and crystallinity, the lower the permeability coefficient and the resulting membrane permeability. See "Permeability and Diffusion Data" Polymer Handbook, 3rd Edition, J. Bradley & E.H. Immergut, J. Wiley, 1989, p. 435. While not being limited to any particular theory, the inventor's believe that, according to this embodiment, the annealing process of this invention enhances significantly the mobility of the amorphous phase interconnecting the crystalline regions of the annealed membranes, thus leading to the enhanced permeability observed from the annealed membranes.

[00052] A preferred embodiment of the present invention is directed to rate controlling membranes used in transdermal drug delivery devices as shown in FIG. 1. In FIG. 1, a transdermal therapeutic system 1 according to this invention comprises a pouch formed from an impermeable backing 2, rate controlling membrane 3, and a contact adhesive layer 4, covered by a removable protective release liner 5. The impermeable backing is configured to provide a central volume which contains a drug reservoir 6 in the form of a gel having dissolved and suspended drug therein. Means other than the in-line contact adhesive layer 4 may be used for maintaining the system on the skin such as a peripheral ring of adhesive outside the path of drug flow from the system to the skin. Adhesive overlays or other fastening means such as belts and elastic arm bands are also contemplated.

[00053] Referring now to FIG. 2, a multilaminate type of transdermal therapeutic system according to this invention is shown. Device 10 comprises a drug reservoir 12 preferably in the form of a matrix containing both the drug and a permeation enhancer, if used, dispersed therein. Reservoir 12 is sandwiched between a backing layer 14, which is preferably impermeable to both the drug and the permeation enhancer mixture, and rate controlling membrane 16. In FIG. 2, the drug reservoir 12 is formed of a material, preferably a polymeric material, that is sufficiently viscous to maintain its shape. The device 10 adheres to the surface of the skin 17 by means of the contact adhesive layer 18. With certain formulations, an adhesive overlay or other fastening means may be preferable to the in-line contact adhesive. The adhesive for layer 18 should be chosen so that it is compatible with system components and the skin and does not interact with the drug or other system component in any way to alter functionality. The adhesive layer 18 may optionally contain enhancer and/or drug. A removable liner (not shown) is normally provided along the exposed surface of adhesive layer 18 and is removed prior to application of device 10 to the skin 17.

[00054] Figure 3 illustrates another embodiment of the invention, device 20, shown in placement on the skin 27. In this embodiment, the transdermal drug delivery device 20 comprises multi-laminate drug formulation/enhancer reservoir 21 having at least two zones 22 and 24. Zone 22 consists of a drug reservoir substantially as described with respect to FIG. 2. Zone 24 comprises a permeation enhancer reservoir which is preferably made from substantially the same matrix as is used in zone 22. Zone 24 comprises a permeation enhancer dispersed throughout and is free of any drug in excess of saturation. Rate-controlling membrane 23 for controlling the release rate of the permeation enhancer from zone 24 to zone 22 is placed between the two zones. A rate-controlling membrane (not shown) for controlling the release rate of the enhancer and/or drug from zone 22 to the skin may also optionally be utilized and would be present between the skin 27 and zone 22.